89. (New) The molecule of claim 4, wherein the second molecule is bryodin.

B10

90. (New) The protein of claim 83 which is fused to bryodin.

91. (New) The molecule of claim 87 which is fused to bryodin.

REMARKS

Prior to the amendments made herein, claims 1-9, 21-25, 34-36 and 38-68 were pending in the instant application.

Claims 40, 41, 45 and 46 have been canceled without prejudice to Applicants' rights to pursue the canceled claims in one or more related applications.

Claims 1, 4, 6, 8, 9, 21-24, 36, 44, 47-54, and 57 have been amended and new claims 69-91 have been added to more particularly point out and distinctly claim that which Applicants regard as the invention. The amendments are fully supported by the specification as set forth in the table below. No new matter is added.

Claim(s)	Support in Specification
1	page 12, lines 28-32; page 25, lines 25-30; and page 36, line 6
4	page 12, lines 28-32; page 25, lines 25-30
6	page 36, line 6
8	page 54, lines 6-8; page 36, line 6
9	page 54, lines 6-8; page 36, line 6
21-24	page 54, lines 6-8; page 36, line 6
36	page 54, lines 6-8; page 36, line 6
44	page 30, lines 27-31; page 12, lines 28-32; page 25, lines 25-30; and page 36, line 6
47-54	page 54, lines 6-8
57	page 12, lines 28-32; page 25, lines 25-30; and page 36, line 6
69	page 13, lines 3-7; and page 36, line 6
70	page 13, lines 12-16

page 13, lines 23

Claim(s)	Support in Specification
71, 74, 79, 87	page 21, lines 15-17
72, 73, 77, 78, 81,	page 13, line 25
75, 82, 84	page 25, lines 25-28
76, 85,	page 25, lines 25-28
80	page 27, lines 32-34
83	page 30, lines 27-31; page 12, lines 28-32; page 25, lines 25-30; and page 27, lines 25-26
86	page 30, lines 27-31; page 12, lines 28-32; page 25, lines 25-30; and page 36, line 6
88	page 12, lines 26-32
89-91	page 34, line 3

INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella for the courtesy of the recent interview in connection with the above-identified application. Pursuant to 37 C.F.R. § 1.133 and M.P.E.P. 713.04, Applicants present this interview Summary Record of the interview of February 7, 2002 ("the Interview") between Supervisory Patent Examiner Anthony Caputa and Examiner Karen Canella, Applicants Dr. H. Perry Fell and Dr. Joseph A. Francisco, and Applicants' representatives, Adriane M. Antler and Muna Abu-Shaar, in connection with the above-referenced application. During the Interview, the outstanding Office Action was discussed.

The rejection in the instant Office Action under 35 U.S.C. § 112, first paragraph, for lack of enablement, due to the term "one or more substitutions or insertions in the primary amino acid sequence relative to that of the monoclonal antibody S2C6" was discussed. Dr. Antler proposed deleting this term in order to obviate the rejection. The Examiners indicated agreement with this strategy. Applicants and Applicants' representatives also presented arguments as to why the instantly claimed invention was not made anticipated or obvious by the prior art relied upon by Examiner Canella in the instant Office Action. Details of these arguments are presented below. Applicants further pointed

out to Supervisory Patent Examiner Caputa and Examiner Canella that, with respect to the rejection of certain claims under 35 U.S.C. § 112, first paragraph, for lack of enablement on the basis that insufficient assurances under 37 C.F.R. §§ 1.801-1.809 had been given regarding the deposit of the hybridoma deposited with the ATCC and assigned accession number PTA-110, the appropriate assurances had been given by way of a Statement of Attorneys for Applicants Regarding Permanence And Availability of Deposited Microorganisms submitted in connection with the present application on April 18, 2001. Examiner Canella located this statement in the PTO's file at the Interview, and indicated that the rejection was thus obviated. Finally, Supervisory Patent Examiner Caputa and Examiner Canella brought to Applicants' attention a potential prior art reference by Pound *et al.* (1999, International Immunology 11(1):11-20; "Pound"). Applicants discussed with the Examiners reasons why, based on the data disclosed therein, the Pound reference does not anticipate or render obvious the presently claimed invention. At the request of Examiner Canella, Applicants present those reasons hereinbelow.

DRAWINGS

Applicants note the objection to the drawings for the reasons set forth in the form PTO-948. In response to the objection, Applicants submit herewith formal drawings in connection with the above-identified application. Applicants thus request that the objection to the drawings be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN

Claims 1, 3, 7-9, 21-25, 36 and 38-68 are rejected under 35 U.S.C. § 112, first paragraph, allegedly because the specification does not provide enablement for a protein comprising "one or more substitutions or insertions in the primary amino acid sequence relative to that of the monoclonal antibody S2C6, or a protein variant of S2C6." The Examiner further states that one of skill in the art would not be able to produce variants of S2C6 having similar properties to the native antibody because of a "lack of guidance of mechanism by which the antibody induces an antineoplastic effect."

Applicants respectfully assert that, for the reasons made of record in the Amendment dated April 18, 2001, the claims reciting "comprises one or more substitutions or insertions in primary amino acid sequence relative to native monoclonal antibody S2C6

as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110" are fully enabled in view of the specification and the state of the art regarding recombinant antibody technology.

However, without agreeing in any way with the Examiner's rejections, and merely to expedite prosecution, claims 1, 8, 9, 21-24 and 44, which recite the limitation that a molecule comprises "one or more substitutions or insertions in primary amino acid sequence relative to native monoclonal antibody S2C6 as secreted by the hybridoma deposited with the ATCC and assigned accession number PTA-110" have been amended to delete such language. Accordingly, Applicants submit that the rejection is obviated.

The Examiner has rejected claims 1, 6, 8, 9, 21-24, 44 and 45 under 35 U.S.C. § 112, first paragraph, for lack of enablement, as a result of an alleged failure to provide sufficient assurance that the conditions of 37 C.F.R. §§ 1.801-1.809 have been met with respect to the hybridoma deposited with the ATCC and assigned accession number PTA-110.

In response to this rejection, Applicants respectfully point out to the Examiner that a "Statement of Attorneys for Applicants Regarding Permanence And Availability of Deposited Microorganisms," which provides the requisite assurances, accompanied by a copy of the relevant International Form of deposit receipt from the ATCC, has already been submitted in connection with the above-identified application. A copy of this Statement is attached hereto as Exhibit C. Examiner Canella located this Statement in the PTO file of the above-identified application during the Interview.

In view of the foregoing, Applicants believe this rejection under 35 U.S.C. § 112, first paragraph, is moot and should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

The Examiner has maintained the rejection of claims 1, 2, 3, 7, 8, and 34 under 35 U.S.C. § 102(b) as being anticipated by Kwekkeboom *et al.*, 1993, Immunology 79:439-44 ("Kwekkeboom") under the doctrine of inherent anticipation. Similarly, the Examiner has maintained the rejection of claims 1, 2, 3, 7, 8, and 34 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,874,082 to de Boer ("de Boer"), under the doctrine of inherent anticipation. The Examiner's basis for the rejections is that these references disclose anti-CD40 antibodies that are not S2C6, which therefore must comprise

one or more substitutions or insertions relative to S2C6. Applicants respectfully traverse this rejection.

In connection with the outstanding rejections under 35 U.S.C. § 102, Applicants note that all independent claims as will be pending following entry of the amendments made herein (*i.e.*, claims 1, 4, 8, 9, 21-24, 36, 44, 69, 80, 83, and 86) recite a structural or functional limitation that distinguish the claimed antibodies from the antibodies of de Boer and Kwekkeboom.

Functional Characteristics of the de Boer Antibodies vs. The Claimed Antibodies

de Boer and Kwekkeboom describe a class of antibodies, including the monoclonal antibodies 5D12, 3C6, and 3A8, which prevents the growth and differentiation of B cells. These antibodies (referred to hereinafter as "the de Boer antibodies") are characterized in the de Boer patent as "blocking the CD40-CD40 ligand interaction" (*de Boer* at Column 12, line 67 through column 13, line 1). This blocking activity is clearly in the context of cell surface CD40 on B cells, as the blocking assays of de Boer measured the inhibition of T-cell-induced B-cell proliferation (*de Boer* Example 5, columns 18-19). This characteristic of the de Boer antibodies is confirmed in other published studies (see Kwekkeboom *et al.*, 1994, Eur. J. Immunol. 24:508-517, submitted as reference BQ of the Third Supplemental Information Disclosure Statement, with particular attention to Section 3.5 on pages 512-513). Thus, the de Boer antibodies clearly do not increase the binding of CD40 ligand to cell surface CD40 on B cells. Because the de Boer antibodies do not increase the binding of CD40 ligand to cell surface CD40 on B cells, de Boer and Kwekkeboom could not possibly anticipate any of claims 9, 21, 22, 23, 24, 36 or 69, because all of these claims are directed to a molecule which, *inter alia*, increases the binding of CD40 ligand to cell surface CD40 on B cells.

Structural Characteristics of the de Boer Antibodies vs. The Claimed Antibodies

de Boer and Kwekkeboom also do not anticipate the other independent claims, which recite structural characteristics or a combination of structural and functional characteristics that would impart to the claimed molecules an epitope specificity akin to that of S2C6 rather than to that of the de Boer antibodies.

As discussed above, S2C6 and the de Boer antibodies are functionally distinct. Based on the distinct functional characteristics of S2C6 and the de Boer

antibodies, one of skill in the art would conclude that the epitope specificity of the de Boer antibodies is different from that of S2C6. Because the heavy chain CDRs are determinants of epitope specificity, one of skill in the art would also conclude that the de Boer antibodies do not comprise SEQ ID NOS:8, 9 and 10, which correspond to heavy chain CDRs 1, 2 and 3 of S2C6, respectively, nor would they comprise SEQ ID NO:7, which is the heavy chain variable region of S2C6 comprising all three heavy chain CDRs. Indeed, as discussed in the Amendment of April 18, 2001, the sequence of de Boer's 5D12 antibody was compared to that of S2C6, and was shown to have 20, 29.4 and 0% sequence identity in the three heavy chain CDRs (corresponding to SEQ ID NOS:8, 9 and 10, respectively).

Given the foregoing, one of skill in the art would conclude that neither de Boer nor Kwekkeboom anticipates claims 1 and 4, which are directed to molecules comprising SEQ ID NOS:8, 9, and 10, *i.e.*, the heavy chain CDRs of S2C6, or claims 8 and 80, which are directed to molecules comprising SEQ ID NO:7, which is the heavy chain variable region of S2C6 and comprises all three heavy chain CDRs.

In addition, one of skill in the art would further conclude that neither de Boer nor Kwekkeboom anticipates claims 44 and 83, because, *inter alia*, the molecules claimed in claims 44 and 83 have a close structural relatedness with S2C6, that is they have regions of at least 80% sequence identity to the heavy chain CDRs of S2C6 (and thus can only deviate by a single amino acid from the first and third heavy chain CDRs of S2C6, and at most by three amino acids from the second heavy chain CDR of S2C6). Similarly, one of skill in the art would further conclude that neither de Boer nor Kwekkeboom anticipates claim 86, because, *inter alia*, the molecules claimed in claim 86 not only have a close structural relatedness with S2C6, that is having at least two heavy chain CDRs of S2C6, but also compete with S2C6 for binding to CD40.

For the same reasons that neither de Boer nor Kwekkeboom anticipates the independent claims discussed above, the dependent claims are also not anticipated by de Boer or Kwekkebooom.

In view of the foregoing, Applicants assert that the de Boer antibodies are not the same as, and therefore neither de Boer nor Kwekkeboom anticipates, the presently claimed invention of any of the claims as will be pending following entry of the amendments made herein. Applicants thus request that the rejections of claims 1, 2, 3, 7, 8 and 34 under 35 U.S.C. § 102 be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Maintained Claim Rejections

Claims 1, 2, 3, 4, 7, 8, and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Kwekkeboom in light of Uckun *et al.*, 1990, Blood 76:2449-2456 ("Uckun") for reasons of record, *i.e.*, that Kwekkeboom allegedly teach antibodies within the scope of the present claims, and "Uckun teaches anti CD40 antibodies fused to non-immunoglobulin proteins," rendering it obvious for one of skill in the art to fuse the antibodies of Kwekkeboom with a non-immunoglobulin protein.

As pointed out to the Examiner in the Amendment of April 18, 2001, it is improper to reject claim under 35 U.S.C. § 103 based on the inherent properties of a prior art reference:

> The rejection of claims 1, 2, 3, 4, 7, 8, and 34 over Kwekkeboom [], which is based upon inherent anticipation by Kwekkeboom [], is improperly raised under 35 U.S.C. § 103 and must be reversed, since § 102 is the statutory section under which inherent anticipation is properly raised. (Citations omitted).

Even assuming, *arguendo*, that it is proper for the Examiner to apply the inherent properties of a prior art disclosure to an obviousness rejection, the rejection of the present claims under 35 U.S.C. § 103 as being obvious over Kwekkeboom in combination wither other references cannot stand for the reasons discussed below.

To establish a *prima facie* case of obviousness, the teachings of the prior art must provide one of ordinary skill in the art with some suggestion or motivation to make the claimed composition. *In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). For a claimed invention to be deemed obvious in view of a prior art disclosure, the prior art disclosure must, firstly, give rise to a *suggestion of or motivation* for the claimed subject matter. Assuming such a suggestion or motivation is found, and the invention is thus arguably "obvious to try" to achieve, only then does one reaches the question of whether one of ordinary skill in the art would have had a reasonable expectation of success in achieving it. *See e.g.*, *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

However, as discussed above in response to the rejections under 35 U.S.C. § 102, the antibodies of Kwekkeboom are functionally and/or structurally distinguished from the claimed molecules, and there is nothing in Kwekkeboom that suggests or motivates the

claimed invention. Thus, not even the threshold inquiry of the test for determining whether a claimed invention is obvious is met.

Uckun does not remedy the deficiencies of Kwekkeboom. Not only does Uckun not provide a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, anti-CD40 molecules that comprise SEQ ID NOS:8, 9 and 10, or anti-CD40 molecules with regions of at least 80% sequence identity to SEQ ID NOS:8, 9 and 10, Uckun does not make a hint or suggestion of such anti-CD40 molecules that further comprise a non-immunoglobulin fusion partner. Therefore, Applicants respectfully submit that the rejection under 35 U.S.C. § 103 (a) of claims 1, 2, 3, 4, 7, 8, and 34 in view Kwekkeboom, further in view of Uckun, has been obviated and should be withdrawn.

Claims 2, 3, 4, 5, 7, 8, and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Kwekkeboom in light of Uckun, further in view of U.S. Patent No. 5, 597,569 to Siegall ("Siegall"). Siegall teaches an antibody-bryodin 2 fusion protein. However, Siegall does not remedy the deficiencies of Kwekkeboom and/or Uckun, discussed above. Specifically, Siegall does not provide a hint or suggestion of anti-CD40 molecules comprising SEQ ID NO:7, anti-CD40 molecules that comprise SEQ ID NOS:8, 9 and 10, or anti-CD40 molecules with regions of at least 80% sequence identity to SEQ ID NOS:8, 9 and 10, whether or not such molecules further comprise bryodin. Thus, Applicants respectfully assert that the rejection of claims 2, 3, 4, 5, 7, 8, and 34 over Kwekkeboom in light of Uckun, further in view Siegall, is in error and respectfully request that it be withdrawn.

Claims 1, 2, 3, 6, 7, 8 and 34 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over de Boer. de Boer teaches a humanized form of the murine anti-CD40 antibody 5D12, and further suggests that any of the de Boer antibodies can be humanized. The Examiner, inferring that the suggestion of humanization extends to S2C6, concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to make humanized forms of S2C6. Applicants believe that this conclusion is erroneous for the reasons discussed below.

To reiterate that which is already of record, the statement by de Boer at column 20, lines 41-45 that "any of the anti-CD40 monoclonal antibodies of this present invention are capable of being humanized using...techniques as applied to monoclonal antibody 5D12," is directed not to S2C6, but to the de Boer antibodies, *e.g.*, 5D12, 3A8 and 3C6. The binding of the de Boer class of antibodies to CD40, in contrast to S2C6,

"prevents the growth or differentiation of the [normal] B cell." *de Boer* at column 3, lines 15-16. (Emphasis added). According to de Boer, this inhibitory property makes these antibodies useful to treat disorders characterized by overproduction of antibodies, such as autoimmune disorders. *de Boer* at column 3, lines 6-8 and 52-54.

Thus, de Boer does not suggest the humanization of anti-CD40 antibodies such as S2C6 which promote proliferation of normal B cells. In fact, such promotion of B cell growth as exhibited by S2C6 would, if anything, dissuaded the skilled artisan from expecting any therapeutic efficacy of S2C6 i*n vivo* due to the danger of promoting undesirable, *e.g.*, neoplastic, B cell proliferation. Not until Applicants' discovery of S2C6's surprising anti-tumor activity and ability to increase the binding of CD40L to CD40 was there any appreciation in the art that S2C6 could be used to inhibit cancer growth, and therefore the motivation for humanization of S2C6 did not exist until the present invention was made.

Accordingly, Applicants respectfully assert that the rejection of claims 1, 2, 3, 6, 7, 8 and 34 under 35 U.S.C. § 103(a) over de Boer are improper and should be withdrawn.

New Claim Rejection

Claims 1-9, 21-25, 34, 36 and 38-68 are rejected under 35 U.S.C. § 103(a), allegedly as being unpatentable over Hirano *et al.*, 1999, Blood 9:2999-3007 ("Hirano") in light of Bjork *et al.*, 1994, Immunology 83:430-37 ("Bjork"). According to the Examiner, Hirano teaches the inhibition of human breast carcinoma cells expressing the CD40 receptor by a soluble CD40 ligand," and Bjork teaches "that the antibody S2C6 positively cooperates in the binding of CD40 ligand to CD40 receptor," thereby concluding that it would be obvious for one of skill in the art to combine the teachings of Hirano and Bjork to arrive at the claimed invention. Applicants respectfully disagree for the reasons discussed below.

Applicants respectfully point out that the present rejection is based on a mischaracterization of Bjork. Contrary to the Examiner's assertion that Bjork teaches that S2C6 and CD40 ligand cooperate for binding to CD40, Bjork teaches that S2C6 inhibits the binding of CD40 ligand (referred to in Bjork as CD39) to CD40 (*see* page 434, right hand column and Table 4). The CD40 used in Bjork's binding assay is a soluble CD40 protein

immobilized on a solid surface.[1] The cooperativity referred to by Bjork (see abstract) is the potentiation by S2C6 of the effect of CD40 ligand on IL-4-induced proliferation of B cells, thereby increasing the proliferation of B cells (*see* page 433 and Table 2). One of skill in the art would not conclude that this potentiation is attributable to S2C6 promoting the binding of CD40 ligand to CD40, because S2C6 can promote the proliferation of normal B cells in the absence of CD40 ligand (*id.*).

While Hirano does teach that CD40 ligand inhibits the growth of breast cancer cells, Hirano does not teach that an anti-CD40 antibody having the characteristics of S2C6 can be useful to treat cancer. Bjork does not remedy the deficiency of Hirano; if anything, Bjork teaches away from the presently claimed invention since it teaches that S2C6 inhibits binding of CD40 ligand to CD40 and increases proliferation of B cells. One of skill in the art would expect, given the teaching of Bjork described above, that S2C6 might promote cellular proliferation, thereby nullifying the beneficial effect of the CD40 ligand administration to cancer patients taught in Hirano.

Accordingly, Applicants submit that the rejection of claims 1-9, 21-25, 34, 36 and 38-68 under 35 U.S.C. § 103(a), allegedly as being obvious over Hirano in light of Bjork has been obviated and should be withdrawn.

THE POUND REFERENCE

During the course of the Interview on February 7, 2002, Supervisory Patent Examiner Caputa and Examiner Canella brought to Applicants' attention a newly discovered reference by Pound *et al.*, 1999, International Immunology 11:11-20 (attached as reference BP of the Third Supplemental Information Disclosure Statement submitted herewith). In particular, Pound describes experiments comparing certain characteristics of the anti-CD40 antibody 5C3 with those of S2C6.

As Applicants pointed out to the Examiners during the interview, the experiments of Pound show that 5C3 is clearly distinct from the presently claimed molecules. Where the binding activities of S2C6 and 5C3 were compared by Pound, S2C6 and 5C3 behaved in a dramatically distinct manner under the same conditions. In particular, the Examiner's attention is directed to Table 1 of Pound, which compares the effects of

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[1] Applicants believe that the use of a soluble CD40 immobilized on a solid surface in the assay may account for Bjork's results (in contrast with the cell surface CD40 recited in certain of the instant claims).

various antibodies on the binding of CD40 ligand on the surface of T cells to a soluble CD40-immunoglobulin fusion protein ("CD40-Fc") (NOT to cell surface CD40 on B cells). Also compared were the effects of various anti-CD40 antibodies on the binding of S2C6 to cell surface CD40.

Where the effect of the various antibodies on the binding of CD40 ligand to soluble CD40-Fc was examined, the CD40-Fc was preincubated with the test antibody, and the ability of the test antibody-CD40-Fc complex to bind to CD40 ligand on activated T cells was measured relative to CD40-Fc preincubated with a test antibody to bind to CD40 ligand on activated T cells (see section entitled "Inhibition of binding of soluble CD40 to CD40L on T cells" at page 12, right hand column). Where the effect of the various antibodies on the binding of S2C6 to cell surface was examined, resting B cells were preincubated with the test antibody, after which time the cells were incubated with S2C6. The ability of the pre-bound test antibody to inhibit S2C6 binding to the resting B cells was measured (see section entitled "Inhibition of binding of CD40 mAb S2C6 to CD40 on B cells" at page 13, left hand column).

Under these experimental conditions, S2C6 inhibited CD40-Fc binding to CD40 ligand on T cells by approximately 82%, whereas 5C3 increased the binding of CD40-Fc to CD40 ligand on T cells by approximately 32% (Table 1, first line of data). These data provide conclusive evidence that S2C6 and 5C3 have different epitope specificities, and therefore could not share the same or closely related set of heavy chain CDRs. Furthermore, binding of 5C3 to B cells did not preclude to a significant degree (22%) the subsequent binding of S2C6 to cell surface CD40 (Table 1, second line of data), indicating that CD40 can simultaneously bind to S2C6 and 5C3. This provides yet further evidence that the two antibodies are distinct both functionally and structurally.

CONCLUSION

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the present application. The Examiner is invited to contact the undersigned with any questions concerning the foregoing.

Respectfully submitted,

Date: February 28, 2002

Adriane M. Antler 32,605
Adriane M. Antler (Reg. No.)

By: Muna Abu-Shaar
Muna Abu-Shaar
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PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090